

Bipolar Network News

Clinical Trials Update

Volunteers Sought for Pilot Level III Outreach Studies

We are seeking particularly well-motivated patients and physicians who wish to help us pilot the Bipolar Treatment Outcome Network clinical trials program in clinical practice settings (Level III). This program is designed to conduct studies in parallel to those conducted on a double-blind, randomized basis in academic centers (Level I). Level III would utilize nonblind randomized methodology with a minimum of ratings and paperwork from the treating physician, along with a modicum of effort from patients who will assist in more detailed description of their longitudinal course of illness and response to treatment. This Level III outreach program is designed to eventually recruit a large number of bipolar patients into clinical research studies so that more rapid and extensive data can be acquired than is currently possible with the more intensive double-blind studies at Level I in the academic centers.

In this current pilot phase of Level III protocols, we wish to enroll patients with their physician's support who would be willing to help assess the practicality and feasibility of such open clinical studies in traditional treatment settings. Patients with inadequately responsive bipolar illness, or their physicians, who wish to participate in open randomized clinical trials at crucial treatment decision points in their illness are requested to contact Tina Goldstein at 301-496-6827 for further information. The purpose would be to help better define which are the best drug treatment approaches to a given phase of illness when no controlled information exists — that is, which of several potentially good interventions actually works most effectively.

Briefly, a series of structured clinical trials are available for patients either with depression breaking through current mood stabilizer treatment or inadequately controlled mania or cycling.

Antidepressant (AD) Comparisons:

(1) In the first antidepressant open study, we are comparing the acute and long-term antidepressant effects of bupropion (with its dopaminergic mechanisms), sertraline (with its serotonergic mechanisms), and venlafaxine (with its combined noradrenergic and serotonergic mechanisms) when added to mood stabilizer treatment (i.e., lithium, carbamazepine, valproate, etc.). Responders to a ten week trial with these medications would be offered a further year of continuation treatment (prophylaxis) in order to ascertain long-term prevention of depressive relapses

and lack of precipitation of mania. Inadequate responders to these drugs would be re-randomized to the other two agents.

(2) If a patient does not respond to these agents, they would be offered open treatment with either tranylcypromine (Parnate[®], a monoamine oxidase inhibitor) or the new potentially mood stabilizing anticonvulsant lamotrigine (Lamictal[®]). Early data from studies with lamotrigine have shown very promising antidepressant characteristics.

Antimanic (AM) and Anticycling (AC) Comparisons:

(1) If patients are experiencing difficulties with mania or cycling despite conventional mood stabilizer treatment, we are also comparing the efficacy of lamotrigine (Lamictal[®]) with gabapentin (Neurontin[®]) as add-on treatments. Lamotrigine limits over-excitation by inhibiting glutamate release, while gabapentin enhances GABAergic inhibitor mechanisms.

(2) For those who wish an entirely new approach, a nonrandomized direct assignment to a new anticonvulsant, topiramate (Topamax[®]), is also available. We are particularly interested in assessing the potential mood stabilizing effects of this agent when used as an adjunct because of its unique mechanism of action and side-effects profile. Topiramate directly blocks one type of glutamate receptor (the AMPA receptor), which is thought to be involved in sustaining increases in neural excitability that may be inappropriate in affective and seizure disorders. Only a few isolated case reports suggest the potentially promising effects of this drug in psychiatric patients, although it is approved for epilepsy adjunctive treatment. In contrast to many of the other agents available for potential mood stabilization, this drug has shown the positive side effect of weight loss. Thus, we wish to rapidly assess the potential effectiveness of topiramate on mood and its utility for weight loss.

(Continued on page 2)

In This Issue:

Clinical Trials Update.....	1
Research Update: Brain Imaging.....	2
Life Chart Highlights: Predictors of Response..	4
Meeting Update: The 2 nd International Conference on Bipolar Disorder.....	7
Around the Network: The Stanford Site.....	11

(Continued from page 1)

Topiramate is generally well tolerated in patients with seizure disorders, with several exceptions. A small percentage of patients report psychomotor slowing and difficulties with word finding with this agent, and approximately 1% of patients develop kidney stones because of the drug's additional actions as a carbonic anhydrase inhibitor. Should the kidney stones develop despite increased fluid intake, patients and physicians should know that the stones that form on this drug are made of calcium and, therefore, subject to rapid destruction with lithotripsy (high-frequency sound waves) that can be administered in an emergency room and thus provide rapid pain relief.

(3) Another treatment that is available for patients with manic and cycling disorders refractory to conventional mood stabilizers is the adjunctive use of the atypical neuroleptic olanzapine (Zyprexa®). This atypical neuroleptic has a structure and mechanism of action most closely resembling those of clozapine (Clozaril®), but without some of clozapine's problematic side effects. In contrast to clozapine it does not cause agranulocytosis and therefore does not require regular blood monitoring. Clozapine shows considerable efficacy in treatment-refractory, rapid cycling, and dysphoric manic patients, and we wish to assess the efficacy of the closely-related agent olanzapine in these types of bipolar illness. ■

Bipolar Network News

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RESEARCH UPDATE: Brain Imaging in the Biological Psychiatry Branch, NIMH

Methods Available

There is now considerable promise that the revolution in brain imaging will begin to have clinical payoffs in the near future, perhaps early in the next century. The ability to



assess brain function in awake patients at baseline resting conditions, during neuropsychological tasks or drug challenges, has now reached an advanced phase of research, with ultimately several potentially direct clinical benefits. Positron emission tomography (PET) scans can be performed to assess cerebral metabolic rate in discrete regions of the brain utilizing deoxyglucose or a closely related measure of cerebral blood flow using O¹⁵-labeled water. In addition, functional magnetic resonance imaging (fMRI) scans are available which can assess blood flow without using any radiation whatsoever. Moreover, magnetic resonance imaging spectroscopy (MRS) techniques can also provide data on brain chemistry, such that measures of brain magnesium and electrolytes, choline and related membrane phospholipids, N-acetyl-aspartate (NAA, which is a potential marker of neuronal dysfunction or loss), and glutamate and GABA are now possible with this technology.

Given these latter possibilities, for example, it is hoped that measurement of deficiencies or excesses in brain glutamate and GABA can ultimately be used to better target illness with the most appropriate treatments, such as carbamazepine, lamotrigine, and topiramate (which inhibit or block glutamate mechanisms via different actions), or GABA-active agents such as valproate or gabapentin (for increasing inhibition). While there are currently no direct data to test this proposition, there are preliminary data indicating that differences in brain metabolism or blood flow assessed by PET may eventually be used in more rapidly matching individual patients to appropriate treatment regimens.

Possible Use in Prediction of Clinical Response: Carbamazepine (Tegretol®) vs. Nimodipine (Nimotop®)

Initial data from the Intramural Program of

the NIMH suggest that patients with frontal hypometabolism are more likely to respond to the dihydropyridine calcium channel blocker nimodipine, while those with hypermetabolism in the context of their equally severe depression are more likely to respond to the mood stabilizing anticonvulsant carbamazepine. These data, described below, were presented by Terence Ketter et al. at the American Psychiatric Association meetings, and are now being prepared for publication. They require extensive replication by other groups before they could be used clinically. Nevertheless, they suggest the potential of this technology to enhance clinical treatment of unipolar and bipolar illness.

Ketter and associates have observed that unipolar patients tend to display the more classical pattern of frontal hypometabolism while bipolar I patients often show patterns of temporal lobe hyperactivity with their depression. Bipolar II patients appear more heterogeneous and can display either pattern. At present it does not appear that these different patterns of cerebral metabolism can be inferred or derived from the clinical presentations of the illness, although this remains to be further ascertained as well.

Currently, 26 patients have been studied with PET scans at baseline and subsequent response to carbamazepine, and 20 patients at baseline and in response to nimodipine. The overall response rate to carbamazepine in this subgroup was only 27%. However, if one utilized the cut-off of relative cerebral hypermetabolism compared with age- and gender-matched controls, the response rate would have increased to approximately 50%. Moreover, it was evident that none of the 14 patients with the typical pattern of cerebral hypometabolism at baseline was among the responder group to carbamazepine. If these data were to be replicated, they might suggest that patients with the hypometabolic type of depressive presentation could avoid an unnecessary trial with carbamazepine in lieu of one of the other mood stabilizing agents that appear to be effective in patients with this hypoactive pattern. These might include nimodipine, as indicated here, or, potentially, the newer

(Continued on page 3)

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anticonvulsants gabapentin or lamotrigine, as noted below.

In the current series, if one were to utilize the cut-off of hypometabolism, one could have theoretically increased the response rate from 25% to 36% with the calcium channel blocker nimodipine. Interestingly, one area of the brain — the left insula — showed the best and most linear prediction of clinical response. Hypofunction in this one area correlated with the degree of nimodipine response, and hypermetabolism in the left insula correlated with a better response to carbamazepine.

Again, it must be emphasized that even if these data were replicated in a series of subsequent studies by other laboratories, they still would not provide the kind of definitive prediction of treatment response that is available with use of antibiotics, for example, if the appropriate microorganism is cultured and specific antibiotic sensitivity assessed. Nonetheless, even some assistance with increasing the odds of treatment response would be clinically useful, particularly in relationship to the growing list of potential antidepressant and mood stabilizing compounds where there is little clinical or neurobiological empirical basis for assessing the best order of sequential clinical trials in individual patients for the highest likelihood of response. It should also be noted that PET scans are not currently available except in the context of a few controlled trials.

PET and Other Anticonvulsants, Lamotrigine (Lamictal®) and Gabapentin (Neurontin®)

Even more preliminary are the emerging data of Tim Kimbrell et al. in our group with other potential PET predictors, using baseline O¹⁵ blood flow in relationship to gabapentin and lamotrigine response. In the studies headed by Mark Frye and associates, we have found promising evidence of an initial clinical response in a six-week, randomized, double-blind clinical trial comparing gabapentin, lamotrigine, and placebo. Fifty-three percent of our first 22 treatment-refractory patients showed much or marked improvement on lamotrigine monotherapy, 39% on gabapentin, and, as expected, only 8% on placebo. When responders to these two agents were compared with

nonresponders, their baseline PET scans revealed substantial differences. At baseline, the responders to these agents showed marked decreases in blood flow, particularly in frontal areas of brain, compared with age- and gender-matched volunteers, while this was not evident in the nonresponsive subgroup. The hypometabolism also improved with treatment response.

These findings remain to be confirmed and extended in our ongoing clinical trial, and patients wishing to participate in this protocol should consider having their physicians refer them to the NIMH. We are particularly interested in patients with inadequately controlled bipolar illness who are otherwise medically healthy, have not had prior treatment trials with gabapentin and lamotrigine, and who might be interested in entering this intensive double-blind evaluation and treatment study. Physicians should contact either Mark Frye, M.D. at 301-496-6825 or Gabriele Leverich, L.C.S.W. at 301-496-7180, or write to these individuals at the Biological Psychiatry Branch, NIMH, Building 10, Room 3N212, 10 Center Drive MSC-1272, Bethesda, MD 20892-1272.

PET Imaging and Possible Prediction of Response to rTMS

The third area of hopeful progress is treatment response to repeated transcranial magnetic stimulation (rTMS) of the brain. Again, highly preliminary data of Kimbrell and associates suggest a possible relationship of baseline differences on PET scan and response to rTMS at either high or low frequencies. We have previously reviewed preliminary evidence of the efficacy of rTMS in the BNN, Vol.1, Issue 3. We and now many other investigators continue to have some success with this novel treatment intervention, although the optimal parameters of brain stimulation have not been clearly identified. Thus, we are studying the comparative efficacy of different frequencies of rTMS (1 Hz or 20 Hz) compared with sham rTMS (i.e., when the magnet is aimed away from the head).

In highly preliminary data we have observed that several patients who have shown the best response to low frequency stimulation had evidence of hypermetabolism at baseline, which decreased toward normal following rTMS and clinical improvement. Conversely, several patients with marked cere-

bral hypometabolism at baseline responded to higher frequencies of rTMS in conjunction with increased metabolism towards normal.

Tim Kimbrell, Bob Dunn, Mark George and others in our group, and Eric Wassermann of the Neurology Institute, have followed up on the potential effects of low-frequency rTMS on cerebral metabolism in normal volunteers and have found in two separate studies that 1 Hz rTMS compared with sham rTMS significantly decreases glucose utilization in the frontal lobes, even in normal volunteers. These data, along with the possibility that faster frequencies of stimulation might increase metabolism, again suggest the possibility that, ultimately, different frequencies of rTMS might be more specifically targeted to individual patients based on their type of cerebral abnormality on PET scan, i.e., higher frequency rTMS for depression with low metabolism, and lower frequency rTMS for depression with high basal metabolism.

Also consistent with this perspective are the preliminary data of Una McCann in our Branch of two patients with mood disorder and concurrent post-traumatic stress disorder (PTSD) (*Arch Gen Psychiatry*, in press). A number of investigative groups have reported that PTSD is associated with increased metabolism, particularly in right frontal and temporal areas of the brain, either at rest or when patients are recalling their traumatic events. In two patients also showing this pattern of right side hyperactivity on PET scans, McCann et al. found that one month of low frequency stimulation was associated with notable clinical improvement in association with relative normalization of the cerebral hypermetabolism. Controlled clinical trials are now in progress to follow up on these preliminary observations. Patients with PTSD who wish to volunteer for this series of studies should contact Una McCann, M.D. at 301-402-2947.

In another branch of medicine, orthopedics, the availability of x-rays obviously markedly enhanced the ability to diagnose bone fractures and prescribe appropriate casting or operative procedures, as well as follow bone healing. While it is highly unlikely that the same kind of definitive diagnosis, treatment, and follow-up will ever be available for the more complex brain dysfunc-

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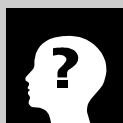
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tions of the neuropsychiatric disorders, current preliminary data from our group and others do, at least, suggest the possibility that the new availability of functional brain imaging techniques may ultimately be converted to assisting in clinical therapeutics for bipolar illness and related affective and anxiety disorders. While PET scans may never become routine, it is much more likely that other less expensive brain imaging techniques such as SPECT scans and functional MRI (which has no radiation) may be substituted for PET scans and be much more widely available for clinical practice.

Many groups throughout the world are following up on the initial studies of rTMS from our group (George et al., 1995, *NeuroReport* 6: 1853-1856; 1997, *Am J Psychiatry*, 154: 1752-1756) and Pascual-Leone et al. (1996, *The Lancet* 348: 233-237) indicating promising effects of 10 to 20 cycles/second (Hz) rTMS over the left frontal cortex. A meeting on rTMS was held in Interlaken, Switzerland in August and an update on that meeting will be presented in the next issue of the *BNN*. ■

Questionnaire on Early Intervention in Childhood Bipolar Illness

The Stanley Network/Early Intervention Initiative (E.I.I.) is looking for families with a **mood disorder on one or 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 to design early intervention protocols for this population.



If you are interested in filling out the questionnaire, please call (301) 496-6827 or 1-800-518-SFBN (7326); send us email: stan-ley@sparky.nimh.nih.gov; or write to: The Stanley Foundation Bipolar Network, 5430 Grosvenor Lane, Suite 200, Bethesda, MD 20814



LIFE CHART HIGHLIGHTS: Differential Response to Carbamazepine vs. Nimodipine: Possible Prediction from Baseline PET Scans

The following retrospective life chart (fig. 1A) illustrates the difficult course of illness of a patient at the NIMH who ultimately showed excellent response to carbamazepine after a poor response to a double-blind clinical trial with nimodipine (fig. 1B). Of interest to our thematic presentation of this issue of the *BNN* on the potential utility of brain imaging in prediction of clinical response, this patient revealed a pattern of hypermetabolism at baseline compared with age- and gender-matched controls (fig. 1C). Thus, this case is an example of the future possibility of better assigning the most efficacious type of treatment based on assessment of the pattern of cerebral metabolism or blood flow at baseline.

Differentiation of tolerance from discontinuation-induced refractoriness

This patient's life chart is also of interest from the perspective that it illustrates an apparent initial excellent response to treatment with lithium in conjunction with antidepressants (from 1985 to 1990), but followed by severe depressive breakthroughs (in 1991 and 1992) despite ongoing lithium treatment. We have observed that 35% of our NIMH-referred lithium-nonresponsive bipolar patients showed this pattern of loss of response (tolerance) to lithium prophylaxis over time. In this and other instances, the patients had indicated that they maintained good compliance. Thus, this type of loss of efficacy does not appear to be based on pharmacokinetics (i.e., related to low blood levels or stopping treatment), but may be related to a loss of drug effectiveness on illness progression, wherein the episodes begin to break through what was previously an adequate treatment.

This tolerance pattern contrasts with the more problematic pattern of loss of response to lithium in patients who are otherwise well maintained and stabilized, who then decide to discontinue treatment and subsequently suffer relapse, as highlighted in the very first issue of the *BNN*. In that patient, and in many others, the resulting new set of episodes occurring in the period of lithium dis-

continuation appeared to lead to subsequent refractoriness to lithium when it had previously been highly effective.

The incidence of this type of lithium discontinuation-induced refractoriness is not known, and it should be pointed out that the majority of patients who discontinue lithium will show renewed responsiveness even if they suffer a relapse. However, even if only a small percentage of patients demonstrate this type of refractoriness, patients should be told that they are at some risk for such an experience if they stop medications that were working well to prevent episode recurrence. That is, in addition to the high risk of relapse upon lithium discontinuation, as noted by Suppes et al. (50% in the first five months off lithium, and 90% by 18 months; 1991, *Arch Gen Psychiatry* 48: 1082-1088), the patient is not necessarily guaranteed the same degree of response that they had previously. Even in the study of Tondo et al. (1997, *Am J Psychiatry* 154: 548-550) indicating that there was no significant difference in clinical course before and after such lithium discontinuation, they note that there was a significantly increased need for concomitant neuroleptic treatment after such discontinuation. This suggests that for most patients, an overall illness deterioration had occurred which required more aggressive treatment following the discontinuation.

In contrast to the phenomenon of lithium discontinuation-induced refractoriness, the patient illustrated in this issue appears to have shown a tolerance pattern despite sustained treatment. The treatment algorithms necessary to approach loss of efficacy via tolerance (versus discontinuation) are not well worked out. Based on some clinical and theoretical data, however, a variety of maneuvers are potentially available in the face of lithium tolerance, which include: (1) the addition of or switching to drugs with different mechanisms of action; or (2) even a renewed trial of lithium at some future date after a period of time on a regimen not including lithium. We postulate that stopping lithium when it has lost efficacy

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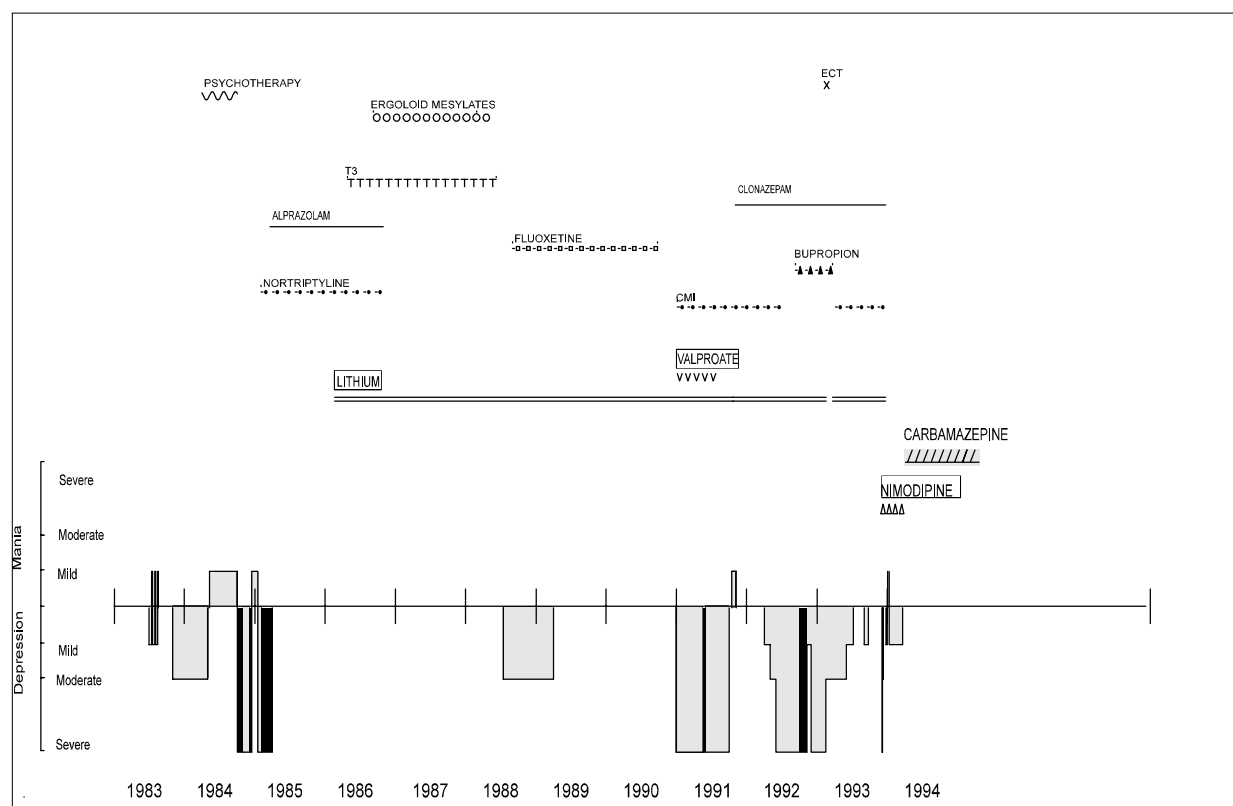


Figure 1A: Course of illness illustrated on the NIMH LCM: Loss of response to lithium(———); nonresponse to valproate (V V V) and nimodipine (Δ Δ Δ); excellent response to carbamazepine (/////)

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may be helpful, in contrast to stopping it when it is still effective, which may have severe consequences.

This patient is representative of the possible positive outcome of switching to a drug such as carbamazepine, which has many mechanisms of action that are quite different from those of lithium carbonate. [For biochemical aficionados only: While both lithium and carbamazepine share some actions on increasing GABA_B receptors in the hippocampus and intracellular second messenger systems at the level of G-proteins and cyclic-AMP, and on inhibition of calcium entry through the *N*-methyl-D-aspartate (NMDA) receptor, as well as increases in substance P levels in the striatum, they exert very different actions on phosphoinositide (PI) turnover, somatostatin, adenosine receptors, and neuropeptide Y (NPY) levels.]

As reviewed in a previous issue of the *BNN* (Vol. 1, Issue 3), there is substantial evidence from more than 15 studies that patients with depression have increased intracellular calcium in their blood elements (either lymphocytes or platelets). On the basis

of these and other data implicating calcium dysregulation in the affective disorders, Dubovsky pioneered the use of the calcium channel blocker verapamil for the potential treatment of manic illness with some success (Dubovsky et al., 1982, *Am J Psychiatry* 139: 502-504). Given the apparent inadequacies of verapamil in the treatment of the depressed phase of the illness, however, we began to pursue the possible better efficacy of another calcium channel blocker, nimodipine, which has some actions that are different from verapamil despite their shared ability to block voltage-dependent calcium channels.

As indicated in figure 1B (a detailed view of this individual's mood ratings at the NIMH), a double-blind trial with nimodipine was not effective for the patient's depression, and may have exacerbated his affective dysregulation with increased periods of dysphoric hypomania in the evening. In contrast, remarkable mood stabilization was achieved when he was switched on a blind basis to carbamazepine, and this improvement has persisted for several years following discharge from the NIMH.

Figure 1C illustrates the general pattern of baseline hypermetabolism on the PET scan of this individual compared with age- and gender-matched normal volunteer controls. It is evident that there is increased metabolism in a variety of brain structures, including medial parts of the temporal lobes. Both decreased and increased activity may be reflective of dysfunction in these areas involved in mood and cognitive regulation. It is particularly noteworthy that this patient was extremely anxious, highly disorganized, and incapable of focused attention during his periods of affective dysregulation, and it appeared that he would not be able to maintain consistent employment because of his extreme cognitive dysfunction. Yet, when he was placed on an appropriate medication (in this case carbamazepine, which generally reduces hypermetabolism in the brains of most patients with affective illness and in those with epileptic disorders), he sustained not only a remarkable improvement in his mood disorder, but also in his cognitive function, and was able to return to active employment. ■

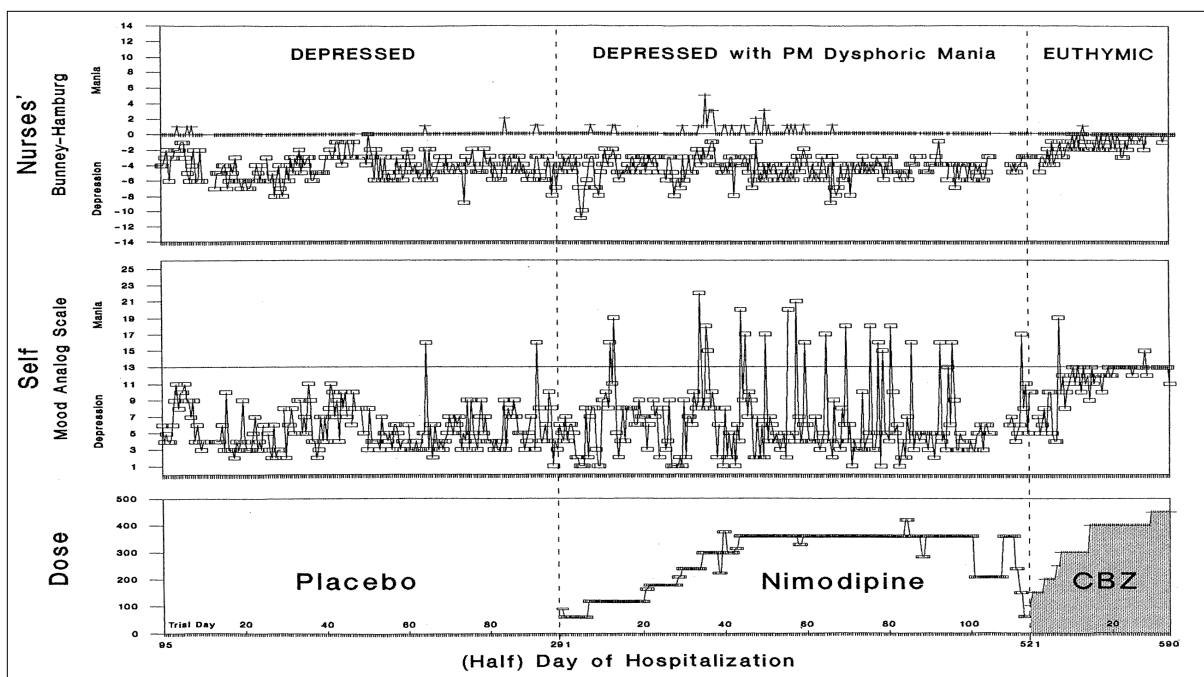


Figure 1B: Nonresponse to nimodipine, excellent response to carbamazepine in a BP II male

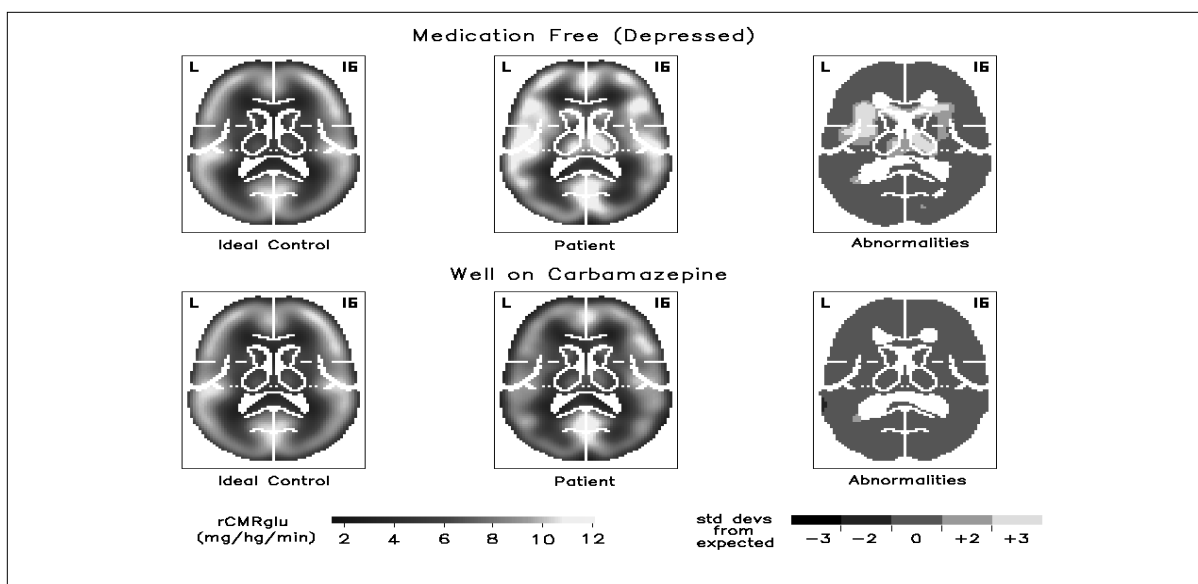
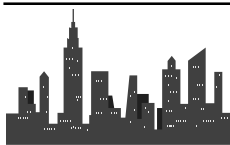
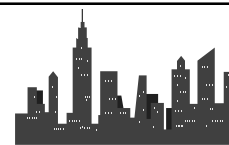


Figure 1C: Baseline hypermetabolism normalized by carbamazepine in a 25-year-old male bipolar patient



Meeting Update: Highlights of the Second International Conference on Bipolar Disorder, June 17-21, 1997, Pittsburgh, PA



The Second International Conference on Bipolar Disorder, held from June 17-21, 1997 in Pittsburgh, opened with presentations by Drs. Jan Fawcett and Alan Gelenberg, both of whom presented data indicating that in a variety of study situations of patients maintained in the community, response rates to lithium are not as high as once expected. In fact, the majority of patients followed for 2 or 3 years on regimens involving lithium (even with adjunctive antidepressant and neuroleptic medication included) suffered a major relapse or the need for rehospitalization. The Coryell 1995 five-year follow up data indicate that 64% were rehospitalized and 50% rehospitalized multiple times.

- In one of the few controlled dose-finding studies, Gelenberg et al. (1989, *N Engl J Med* 321: 1489-1493) observed that higher compared with lower lithium levels were twice as effective for the prevention of episodes, but were associated with a three-times greater incidence of side effects. However, in patients with greater than 3 prior episodes, this higher dose effect was no longer apparent. This study and many others raise the specter that lithium is less effective when prophylaxis is instituted after more than 3 or more prior episodes.

- New data of L.V. Kessing, P.K. Andersen, T.G. Bolwig and P.B. Mortensen from the Denmark registry of 20,350 patients hospitalized for depression, confirm the presence of a sensitization effect of prior episodes on subsequent course of illness. In their study, they found that the incidence and time to rehospitalization for depression were directly proportional to the number of prior hospitalizations for depression. This was true in both unipolar and bipolar patients, and after the fifth unipolar depression, the rates of relapse completely paralleled those of bipolar patients. This is the first large-scale study demonstrating that episodes of affective illness may, in themselves, be of pathophysiological significance, and can increase the vulnerability to subsequent relapses and, potentially, to relative treatment nonresponsiveness. In this Danish registry study, the investigators were able to rule out the alternative interpretation that

there were simply different groups of patients with different vulnerabilities to recurrence, and that their results were predetermined from the outset. Statistically, they showed that this was not the case and that the most likely explanation is that repeated episodes of illness themselves lead to increasing vulnerability to relapse. These and a variety of other data speak strongly to the importance of early intervention and long-term and sustained prophylaxis in order to not only minimize the morbidity and potential mortality of each episode, but also to lessen the impact on the long-term course of illness.

However, it is against this backdrop that one is greatly disappointed with the repeated evidence from a variety of sources (including the recently published National Depressive and Manic-Depressive Association survey, the data of Janice Egeland, and now our own data in the Bipolar Treatment Outcome Network), indicating that patients in the United States experience their first manic or depressive symptoms approximately a decade prior to their first treatment. Thus, earlier recognition and treatment of manic and depressive symptoms is clearly a much needed goal for the general population, since 40% of patients with Bipolar I illness are not in treatment, according to the latest epidemiological survey (Regier et al., 1993, *Arch Gen Psychiatry* 50: 85-94).

Family members with depression can, however, be particularly alert to mood symptoms in their offspring and encourage early institution of effective treatment. This is all the more important since there is evidence of a cohort effect — as well as a greater incidence rate — with earlier onset of affective illness in the general population. In addition, there is evidence in some families, particularly with paternal transmission, of an effect like that of genetic anticipation in Huntington's chorea, wherein the illness can manifest much earlier in successive generations. The Johns Hopkins group (McInnis et al., 1993, *Am J Hum Genet* 53: 385-390) have evidence for such a phenomenon, as noted in the previous BNN and presented again at this meeting.

- The data of M. Strober, J. Biederman, and B. Geller were again presented indicating that there is a subgroup of bipolar patients with very early onset of illness, even in prepuberty. These early onset disorders tend to be accompanied by more chronic illness manifest with extreme lability, including temper tantrums, isolative withdrawal, and comorbid symptoms of Attention Deficit Hyperactivity Disorder (ADHD) in a very high percentage (approximately 90%) of patients. Distinguishing features of mania, in contrast to isolated ADHD, include increased sexual interest/activity, violent nature of aggression, grandiose delusional aspects of thinking, and extreme mood lability. Some academic reviewers in the field still argue about the validity of the diagnosis of mania in very young children, even though all investigators agree that these symptoms can have a devastating impact on the child, the child's family, social relations, and education. Lithium and the mood-stabilizing anticonvulsants have been reported to be effective in uncontrolled studies and, in some instances, appear to require augmentation with psychomotor stimulants for the residual ADHD symptoms. Tricyclic antidepressants are typically ineffective or can exacerbate the course of illness in young children.

- Cognitive behavioral therapy manuals are now being written and developed for illness with childhood onset (just as they have been for adult onset illness [MR Bosco and AJ Rush, *Cognitive-Behavioral Therapy for Bipolar Disorder*, New York: Guilford Press, 1996]), and were presented by Patelis-Siotis, Young, Joffe and associates from Hamilton, Canada. These therapies have multiple targets and potential mechanisms of effectiveness, and include a strong educational component (which reinforces compliance), behavioral approaches to stress reduction, and cognitive approaches to the associated depressive thought disorder. They also have family and interpersonal problem-solving interventions and behavioral homework assignments for beginning to deal with a variety of concepts using a more habit-based memory mechanism.

(Continued on page 8)

(Continued from page 7)

[Editor's Note: This type of repetition and practice appears to be particularly important since depressed patients have relatively selective impairment in their implicit (unconscious, habit) memory systems compared with their explicit (one time) temporal lobe-mediated conscious memory mechanisms (Weingartner et al, unpublished data), suggesting the need for repetition in order to better engage the under-functioning habit (memory) system. It is this system, which normally helps navigate one "on automatic" through a variety of tasks and conceptual approaches, that is even more impaired in depressed patients than typical types of memory paradigms. This provides another potential explanation for depressed patients' subjective complaints of more profound memory deficits than are often evident on traditional tests of explicit or representational memory.]

- Kay Redfield Jamison gave the banquet dinner speech at the conference, describing her experience of going public with her manic-depressive diagnosis. This presentation was exquisitely poignant, particularly with her recitation not only of her own disturbing experiences with the illness and others' responses to it, but also of the tremendous number of parents and patients who have approached her with devastating stories of the effects of this illness on their family's lives. Dr. Jamison's academic, and now heroic personal, contributions to the area of destigmatization of this illness can only be admired and applauded if not emulated. She received a well-deserved standing ovation.

- A series of posters were all convergent in reporting an approximately 50% response rate with adjunctive lamotrigine (Lamictal®) in refractory depression. These studies were all highly congruent with the review by Charles Bowden and associates who focused on the largest and most systematic data with lamotrigine, predominantly as adjunctive therapy but, in several instances, in monotherapy. Again, 50% improvement rates or greater were found in refractory bipolar depression and, notably, this rate was achieved without cycle acceleration or exacerbation of mania. While many of lamotrigine's actions are similar to those of carbamazepine, such as the blockade of sodium channels and subsequent inhibition

of excitatory amino acid (glutamate and aspartate) release, lamotrigine also blocks 5-HT₃ receptors and affects calcium-related mechanisms in cells. These or other yet to be discovered effects clearly give it a very different anticonvulsant psychotropic profile. Like valproate, lamotrigine is effective in most seizure types, as opposed to carbamazepine, which is particularly effective in generalized and complex partial seizures, but may exacerbate petit mal or absence epilepsy. It appears that lamotrigine may also have a different profile of psychotropic actions, because some of our less than adequate responders to carbamazepine had excellent responses to lamotrigine.

- Sue McElroy reviewed evidence of the effects of anticonvulsants in bipolar illness,

Meeting Update:



The Second International Conference on Bipolar Disorder

and in particular endorsed a valproate loading dose strategy for acute mania, with 20-30 mg/kg from the first day of treatment being generally well tolerated. In addition to the promising effects of lamotrigine and gabapentin, she emphasized the need for studying the new add-on anticonvulsant topiramate, with its unusual mechanism of action and side-effects profile, as well as the soon to be approved GABA reuptake inhibitor tiagabine (Gabitril®).

- In an excellent symposium, "New Approaches to the Pharmacotherapies of the Affective Disorders", John Tallman reviewed progress in understanding the benzodiazepine-GABA_A receptor complex, which influences chloride influx into cells, stabilizing them and decreasing increased firing rates. The benzodiazepines, which appear to play an important role as anxiolytics and, increasingly, as agents active at GABA receptors (indirectly by increasing

the amount of GABA in brain), are useful in the treatment of bipolar illness. These include valproate, gabapentin (which works on the L-amino acid transporter), and the anticonvulsant tiagabine. Tallman and associates have dissected the molecular biology of the GABA receptor, hoping to produce a drug with the potent anxiolytic effects of the benzodiazepines without their side effects such as ataxia, sedation, memory problems, and a proclivity for tolerance development.

Much is understood about the increasingly complex subunit composition of the GABA receptor with 6 alpha subunits, 4 beta subunits, 3 gamma subunits, and 2 omega subunits. The subunit composition appears different in different areas of brain, conveys different pharmacological activity, and also appears to differ at different stages of development. Preliminary evidence from our laboratory also indicates that tolerance can selectively change the expression of receptor subunits; in particular, tolerance to the anticonvulsant effects of carbamazepine and diazepam appears to involve a failure of seizures to regulate the alpha-4 receptor subunit of the GABA_A receptor. Thus, the receptor subtype adaptation may be associated with the loss of anticonvulsant, if not psychotropic, efficacy to these compounds over time.

Dr. Tallman has indicated that many subtype-selective agents are available in development, but it is "the little things that get you", such as the kinetic profiles of these compounds, their availability to the CNS, and their potential toxicities and interactions with other agents, that make it very difficult to find an appropriate drug for the clinic. Nevertheless, he remains optimistic that several new compounds from this approach will soon be available in the clinic.

- Perhaps the most exciting presentation of the meeting was that of Dr. Hussein Manji, who took a more direct approach to understanding the mechanisms of action of the mood stabilizing agents that currently exist, attempting to elaborate on some of their common mechanisms of action so that they can be targeted with newer agents. He reviewed the evidence that the intracellular transduction mechanisms between the receptor and other intracellular machinery of the cell, the G proteins, are excellent candi-

(Continued on page 9)

(Continued from page 8)

dates for explaining the mood stabilizing effects of lithium, valproate, and carbamazepine, because these G proteins can amplify receptor effects up to 10,000-fold. Thus, if this amplification process were to go awry and cells remained overstimulated, one could envision this being an important mechanism in both mania and depression. Such a concept also provides a way of understanding the action of a given drug such as lithium on the over swings of both mania and depression. If both are viewed as excesses, either in excitatory systems in mania or in inhibitory systems in depression, then dampening the adenylate cyclase and G protein amplification mechanisms could be of potential therapeutic value. Lithium appears to have inhibitory effects on a variety of intracellular transduction mechanisms, including: (1) PI turnover, (2) cyclic AMP formation, and (3) calcium calmodulin kinase.

Dr. Manji studied the levels of the inhibitory G protein (Gi) in platelets and lymphocytes of patients treated with lithium and found that lithium increased levels of Gi in platelets. More specific studies indicate that even when levels were not affected, lithium significantly increased Gi activity, which would have the effect of dampening overexcited systems. This effect of lithium required chronic administration and persisted for days after the drug was stopped, i.e., characteristics consistent with the clinical pharmacology of lithium in the treatment of affective illness. He presented evidence that lithium stabilized the trimeric or inactive form of the G protein as a specific mechanism. What was also exciting was that valproate achieved some of the same effects, possibly by a slightly different mechanism.

Another target of lithium's action is the phosphoinositol second messenger system in which PIP_2 is broken down to generate two compounds, IP_3 (which modulates intracellular calcium release) and DAG (diacylglycerol) which activates protein kinase C (PKC). PKC is involved in many intracellular transduction mechanisms, including being a key candidate for LTP (long-term potentiation) and other models of learning and memory. Dr. Manji has found that lithium, valproate, ECT, and verapamil all decrease PKC activity and, based on this series of findings, he has used a direct PKC

inhibitor to assess whether this could be a mechanism for these agents' antimanic effects. Tamoxifen, in addition to its effects on estrogen receptors, is a PKC inhibitor, and it is thought that this action could, in part, explain its anticancer effects when used in acute treatment or prophylaxis of breast cancer. Most excitingly, 6 of the first 7 manic patients treated with tamoxifen had a rapid-onset, acute, antimanic response. A new, more selective PKC inhibitor, bryostatin 1, will now be explored by Dr. Manji and associates to see whether it might have similar effects, and thus dissociate the potential PKC versus estrogenic effects of tamoxifen.

Finally, Dr. Manji reviewed his new data indicating that both lithium and valproate increased protein binding to a specific DNA

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activator sequence in cells called AP-1. Lithium did this by increasing phosphorylation of the transcription factor c-jun, while valproate achieved this increase in AP-1 binding by increasing c-jun levels themselves. Thus, the common effect of these two agents in AP-1 binding through slightly different mechanisms could explain their partial, but not entirely overlapping, profiles of clinical efficacy in the mood disorders, as well as establishing another possible target for new drug development.

[Editors Note: Not reviewed in this meeting, but of considerable interest, are the common effects of the antidepressants on increasing the activity of another transcription factor -- cyclic adenosine monophosphate response element binding protein (CREB) (Duman et al., 1997, *Arch Gen Psychiatry* 54: 597-606). These investigators not only confirmed the initial findings of Mark Smith (formerly of our laboratory) that an-

tididepressants administered chronically tended to increase neurotrophic factor gene expression, such as brain-derived neurotrophic factor (BDNF) in the hippocampus, but also a whole series of antidepressants appear to achieve this result via their effects on CREB (Smith et al., 1995, *Proc Natl Acad Sci USA* 92: 8788-8792). What makes these findings particularly exciting is the fact that BDNF is positive in a variety of animal models used to screen for antidepressant activity, and the effects of these antidepressants are opposite to those of some stressors which tend to decrease BDNF in hippocampus. Mark Smith et al. (1995) demonstrated, and Duman et al. (1997) confirmed and extended, the finding that several antidepressants would not only have these opposing effects, but also, if they were administered concurrently with some stressors, could block the stress effect of these agents. Thus, these data provide another contribution to the notion that long-term treatment with antidepressants may have a variety of benefits, particularly in unipolar depression, in which not only would episodes be inhibited, but also possibly some of the deleterious neurochemical effects of stress as well. To the extent that stressor exposure is involved in the precipitation of episodes of mania and depression, as discussed by Constance Hammond at this meeting, one could also envision antidepressants having this action, particularly if they were given concurrently with mood stabilizers to decrease the liability of the antidepressant for causing over swings into the next manic episode.]

Many poster presentations contained interesting and novel data:

- Lori Altshuler reported on increased size of the amygdala in bipolar patients that correlated with the number of prior episodes of mania.
- Bebachuk, Moore, and Manji reported that lithium reduces myo-inositol levels in critical brain regions in patients suffering from bipolar affective disorder, as shown by magnetic resonance spectroscopy studies. Notably, this study is beginning to reveal the possibility of studying brain chemistry directly in patients with illness, and their response to treatment.

(Continued on page 10)

(Continued from page 9)

- Mark Frye, Kirk Denicoff, and others in our group reported that patients treated with a year of lithium had lower free T_4 levels that were correlated with increased severity of depression, suggesting the possibility that overly aggressive treatment with lithium may be depressogenic. These data are convergent with the verbal report by Charles Bowden that valproate was more effective than placebo in treating depression in his long-term prophylaxis study, but that lithium was actually less effective than placebo in this study. Perhaps this was partially related to over-aggressive treatment and/or low free thyroxine (T_4) levels. A prospective study is now being designed in the Stanley Network in order to assess whether thyroid augmentation can ameliorate this lithium effect.

- Horrigan and Barnhill reported six cases of adverse responses among 95 outpatients treated with guanfacine hydrochloride (Tenex[®]), an alpha-2 adrenergic agonist used experimentally for the treatment of ADHD. These patients had states resembling hypomania and mania on doses ranging from 1-2 mg/day. All of these patients had clinical or familial risk factors for bipolar disorder. Therefore, this study is convergent with the data that family history of bipolar illness should lead the clinician to be particularly cautious with approaches to ADHD with stimulants, or in this case, an alpha-2 adrenergic agonist, and clinicians perhaps should, instead, also consider the mood stabilizers.

- A. Konig reported that the antidepressant effects of acute total sleep deprivation could be maintained in a large percentage of subjects if patients went back to sleep at 5 p.m. and slept until midnight after the day of sleep deprivation, and then successively moved their hour of sleep onset forward one hour each day until they arrived at the conventional bedtime of 11 p.m. and slept until 6 a.m. This study is of particular importance as it may be a way to provide acute onset of antidepressant response in unipolar and bipolar depression following sleep deprivation-induced overnight mood improvement. Previously, the large majority of patients relapsed following return to sleep unless they were co-treated with lithium. This combination of one night of total sleep deprivation with a consecutive sleep phase advance may, if replicated, provide a clinically

important new rapid onset antidepressant therapy.

- M. Shetty reported that valproate was able to prevent steroid-induced mood disturbances in a case report, paralleling an earlier similar case report of such an effect with carbamazepine. Both of these case reports raise the possibility that not only lithium, but also other mood stabilizing anticonvulsants will be able to ameliorate steroid-induced mood exacerbations.

- P. Silverstone reported, in a personal communication, that the calcium channel blocker diltiazem was useful in affectively ill patients, raising the possibility that not only the dihydropyridine calcium channel blockers, but also other categories, may ultimately play a role in the treatment of affectively ill patients.

- T. Suppes presented data that clozapine was highly effective in a variety of treatment-refractory bipolar patients. [Preliminary data from other investigators suggest that olanzapine and some of the other atypical agents may play an increasingly important role in bipolar illness, in addition to their treatment profiles in schizophrenia].

- M. Szuba reported on the substantial antidepressant effects of protirelin (TRH) administered at midnight in bipolar depressed patients.

- J. Walden reported that lamotrigine may limit pathological excitation by modulating calcium and increasing fast transient potassium currents or the calcium-dependent potassium current.

- M. Young presented data from a double-blind, placebo-controlled trial comparing the effects of paroxetine and imipramine in the treatment of bipolar depression, in 35 patients randomized to paroxetine, 39 to imipramine, and 43 to placebo for a ten week treatment period. Patients were maintained on either low or high lithium levels. No patients developed mania on paroxetine, while 8.3% did so on imipramine. The placebo rate was not stated in the abstract. Clearly, longer-term outcome data on the liability of paroxetine for inducing mania in bipolar patients is needed, but these initial findings are promising.

- E.G.T.M. Hartong presented the randomized data of Moleman, Nolen, and Hoogduin on a double-blind, multicenter trial of carbamazepine versus lithium prophylaxis for treatment-naïve bipolar pa-

tients. Ninety-eight patients were randomized: of the 41 patients who completed two years, 6 were partial responders, and 18 were nonresponders. There was approximately equal efficacy between lithium and carbamazepine, with results parallel to the Denicoff et al. study (*J Clin Psychiatry*, in press) in less treatment-naïve patients. The Denicoff et al. study indicated that the combination of lithium and carbamazepine was much more effective for rapid cycling patients (50% response rate), compared with less than half this rate for monotherapy with either agent.

- Ketter et al. reported on the combination of bupropion plus an SSRI in treatment-resistant bipolar patients also maintained on a mood stabilizer. Four of 9 patients showed marked improvement, suggesting the possible utility of combination antidepressant treatment targeting different mechanisms of action in treatment-refractory bipolar patients.

- R.H. Yolken and E. Fuller Torrey presented fascinating new data on potential viral and other environmental etiologies of bipolar illness as manifested by a clear seasonality of birth. In addition, they found evidence of a highly significant increase in frontal cortex mRNAs (similar to the X-17 simian virus 5, the X-6 DBL transcription factor, and the X-54 group D retro virus), in patients compared with controls. Viruses could influence the pathogenesis of bipolar illness by affecting genomic mechanisms as well as by inducing immune responses. Yolken reminded us that, initially, the major psychoses of schizophrenia and bipolar illness were not separable from those of infectious agents such as syphilis until the seminal classificatory schema of Kraepelin and others.

A more modern reminder of the possibility of infectious etiology for other medical illnesses (that appeared ridiculous to the untrained observer and even to most gastrointestinal physicians just a decade ago) is that of gastric ulcers. People initially thought that stress caused this recurrent illness, and psychotherapy was recommended. A genetic lineage was postulated and acute response to medications with a high relapse rate was found with the histamine-2 receptor blockers to reduce gastric acidity. It is now clear that the bacterium *helicobacter pylori* is the cause

(Continued on page 11)

AROUND THE NETWORK: THE STANLEY CENTER AT STANFORD

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Terence A. Ketter, Principal Investigator

Terence A. Ketter, M.D., heads the Stanley Foundation center at the Department of Psychiatry and Behavioral Sciences at Stanford University, specially funded by E. Fuller Torrey as part of his overall initiative to enhance multiple independent research efforts in bipolar illness. Dr. Ketter is Associate Professor of Psychiatry and Chief of the Bipolar Disorders Clinic, and has focused the efforts of this Center on the issue of identifying different



Terence A. Ketter, M.D.

pathophysiologies of mood disorders using functional brain imaging and attempting to relate these to treatment response. While this Center is not one of the five sites directly involved in the Stanley Foundation Bipolar Treatment Outcome Network, it is hoped that some of the methodologies will be shared.

Dr. Ketter received his M.D. degree from the University of Toronto, a master's degree in mathematics from the University of Sydney, and served his residency at the University of California at San Francisco. His training in mathematics has been crucial for his development of expertise in the complexities of the hardware and software necessary for acquisition of functional brain images with new technology and methods of highly sophisticated data analysis.

These attributes were brought to the forefront in his work as a clinical associate in the Biological Psychiatry Branch of the NIMH from 1988 to 1995. In his first year, he single-handedly managed all of the administrative, screening, patient care and research functions of the Unit. Dr. Ketter thus emerged from this "trial-by-fire" as one of our most outstanding psychopharmacologists and unit chiefs, and was subsequently able to develop his special expertise in brain imaging.

He, together with Mark George, M.D. (another clinical associate who arrived the next year), helped develop brain imaging methodology in our group. The team of Ketter and George established a large group of healthy volunteers studied by PET (with O^{15} -labeled water for blood flow studies and F-18 deoxyglucose for metabolism) in order to compare and contrast with patients with unipolar and bipolar affective disorders (as described above). His work conclusively demonstrated that the i.v. local anesthetic procaine (Novocaine[®]) was limbic-selective and suggested that affectively ill subjects had altered limbic function. Dr. Ketter played a key role in studying the pharmacokinetics of carbamazepine and valproate, and their interaction with bupropion, as well as formulating and negotiating the methodology for the clinical trials of lamotrigine, gabapentin, and placebo. He was instrumental in the training and career development of a variety of investigators in the brain imaging area, including Brenda Benson, Mark Willis, John Little, and Tim Kimbrell; and in psychopharmacology, including Lauren Marangell, Ann Callahan, and Mark Frye.

As an inveterate "West Coaster", and appreciating the unique qualities of California, Dr. Ketter was lured away to Stanford where he is continuing to investigate a host of themes related to prediction of psychopharmacological response with brain imaging. In his new studies, he has found a remarkably high response rate to valproate monotherapy in treatment-naïve bipolar II patients, and has developed a mood induction paradigm to supplement baseline resting studies in order to ascertain whether either brain imaging procedure might be a suitable predictor of pharmacological response. This procedure of more prolonged depressed mood induction in normal volunteers produces decrements in metabolism in the same frontal and paralimbic structures that tend to be hypofunctional in depression. In contrast, the briefer sad emotion induction pioneered by Mark George induces increases in blood flow in these areas.

At the same time, Dr. Ketter and his collaborators at Stanford are developing new procedures for assessing brain GABA and glutamate by magnetic resonance spectroscopy (MRS). As noted above, it is hoped that measurement of these major excitatory (glutamate) and inhibitory (GABA) neurotransmitter systems will not only allow ascertainment of the differential pathophysiologies of mania and depression, but also help in predicting which patient needs which drugs for optimal response. Dr. Ketter is also pursuing a variety of other themes including the use of antidepressant combinations for treatment-refractory bipolar patients.

Dr. Post and the Biological Psychiatry Branch are deeply indebted to Dr. Ketter for his unique guidance and productivity in the area of psychopharmacology and brain imaging, which would not have been possible without his critical developmental contributions while at the NIMH and now as an ongoing collaborator and consultant from Stanford. We and the field as a whole eagerly await his next generation of studies, that will undoubtedly help illuminate the differential pathophysiologies of affective dysregulation and ultimately assist in better targeting of therapeutics. ■

(Continued from page 10)

of the vast majority of gastric ulcers, and that children are often the cause of ulcers in their parents not via the route of increased stress, but instead by passing on the bacterial infection in their stool. Appropriate antibiotic treatment can be curative with a very low relapse rate compared with the extraordinarily high relapse rate with palliative H-2 blocker treatment. With the modern tools of epidemiology and molecular neurobiology, Torrey and Yolken are one of the few investigative groups exploring this novel route of possible viral pathogenesis in a subgroup of patients with bipolar illness and schizophrenia. The new data were most exciting. ■

Bipolar Network News

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In This Issue:

Brain Imaging to Predict Response
The Second International Conference on Bipolar Disorder
Around the Network: The Stanley Center at Stanford
